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Original Research

Epidemiology in ovarian carcinoma: lessons from autopsy

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Abstract

Objective: We challenge epidemiologic knowledge regarding ovarian carcinoma (OC) by bridging the gap between clinical and autopsy data.

Methods: Autopsy reports, histological slides and clinical files from 660 patients in whom OC was diagnosed from 1975-2005 were studied (autopsy cohort, n=233; Clinical Cancer Registry from the local gynecologic center, n=427).

Results: Out of the autopsy cohort, we identified four distinct subgroups of patients: 1) OC was diagnosed before autopsy, n=156 (67.0%). 2) OC was an incidental finding, n=16 (6.8%). 3) The ovarian tumors were not primary OC but rather metastases from other primary tumors; this revised diagnosis was first made by using current histopathological knowledge/techniques, n=24 (10.3%). 4) Death was directly due to OC in its final stage and OC was first diagnosed by autopsy, n=37 (15.9%); when these cases were added to the Clinical Cancer Registry to an adjusted OC incidence model, the autopsy cases comprised 8.8% of the adjusted cohort and almost doubled the percentage of oldest patients (≥ 80 years at diagnosis) from 4.9% to 9.3% (p=0.013).

Conclusions: Epidemiological data from the 1970s-1990s may overestimate true incidence because up to 10% of carcinomas in the ovary were not properly classified. Patients who were first diagnosed with OC by autopsy comprise a distinct subgroup. These are patients who have not been seen by specialized oncologists and thus play no role in their perception of the disease. Nevertheless, these cases have impact on prevalence and incidence data of OC and in an era of reduced autopsy rates will probably be overlooked.

Keywords: ovarian cancer; autopsy; epidemiology; incidence; prevalence; metastases

Introduction

In developed countries, ovarian carcinoma (OC) is the fifth most frequent cause of cancer death in women and the most lethal gynecologic malignancy [1]. In most cases, the disease is diagnosed in its late stage. Despite current multimodal therapies, most patients cannot be cured. According to WHO estimates in 2012, there are approximately 239,000 new cases annually worldwide, and about 152,000 patients die of the disease [2].

The epidemiologic knowledge regarding the incidence of OC stems predominantly from epidemiological, population-based cancer registries whose aim is to identify all cases from a well-defined regional population, including clinically symptomatic cases as well as autopsy-only detected incidental cases. Histologic verification is considered the gold standard to ensure valid and accurate diagnoses of cancer registry data. In the pre-immunohistochemical era, histopathologic interpretation in cases with suspected OC, especially in case of peritoneal carcinomatosis, was not always unequivocal as other cancers may present a histologic phenotype similar to OC [3-6]. Thus it might be speculated that a substantial proportion of patients might be either falsely assigned as OC (false positive) or true, clinically relevant cases (false negative) may have been missed in the past, thereby introducing bias in long-term trends in OC. In order to get a gross estimate of the suspected bias, we reviewed autopsy reports and clinical records from all cases of OC from 1975-2005 and re-evaluated past histopathologic diagnoses with current immunohistochemical methods. The few studies, which analyzed autopsy data in OC, evaluated exclusively the metastatic patterns of the disease at the time of death [7-12]. To our knowledge, this is the first study which challenges current epidemiologic knowledge regarding OC by bridging the gap between clinical and autopsy data.

Patients and Methods

Between 1975 and 2005, 22,023 female autopsies were performed at the Institute of Pathology of the University of Basel, Switzerland. Of these, primary OC was diagnosed in 233 cases. In

order to avoid heterogeneity, only epithelial tumors, which comprise 90% of all ovarian cancers [13], were considered in the study. Borderline tumors were excluded from analysis.

The autopsy reports and clinical records of these 233 patients, including surgical reports and information on chemotherapy treatment, were reviewed for the following information: date of diagnosis, patient's age at diagnosis, clinical course (including information regarding surgery and chemotherapy), age at death, cause of death, disease-specific survival time (DSS), and patterns of metastatic sites at time of autopsy. The median age of all cases was 70 years (range: 24-98 years). Median DSS was five months (range: 0 to 300 months).

To confirm the histological findings reported in the autopsies, approximately 4,550 microscopic sections were reviewed by a specialized gynecopathologist (G.S.), averaging 20 sections/case.

In cases in which the diagnosis primary OC questionable due to histomorphological features, immunohistochemical tests (antibodies against CDX2, CK7, CK8/18, CK19, CK20, CEA, estrogen receptor, progesterone receptor, WT1, p16 and p53) were performed.

In addition to the autopsy data, we also reviewed the clinical data of 427 patients who were diagnosed and treated for OC in the above mentioned 30-year period at the Women's Hospital of the University Hospital Basel. Data of patients who were diagnosed between 1975 and 1989 were taken from the institutional Gynecologic Cancer registry (index card system). The cases of the patients who were diagnosed after 1990 were recorded in the institutional prospective relational web-based database. The median age of these 427 patients at diagnosis was 60 years (range: 23-91 years).

The study was carried out in accordance with the guidelines of the Ethics Committee of the University of Basel.

Statistical methods: Statistical differences between ages of different subgroups were analyzed using the unpaired t-test. Comparisons between nominal parameters were made with the Fisher exact test. In all statistical tests the level of significance was $p < 0.05$.

Results

Out of the entire autopsy cohort of 233 cases, we identified four distinct subgroups (Table 1):

1. Patients with OC diagnosed before autopsy, n=156 (67.0%).

- One hundred thirty-five cases in which the death of the patient was directly due to OC in its final stage.
- Six patients died within three weeks after primary surgery for OC due to postoperative complications.
- Fifteen patients had known OC, but had other clearly identifiable causes of death based on prior clinical evaluation and confirmed by postmortem examination (non-malignant diseases, n=9; other malignant diseases, n=6).

This largest subgroup of the autopsy cohort had a median age at death of 70 years (range: 24-96 years) and a median DSS of 11 months (range: 1 week-300 months).

2. Patients with OC as an incidental finding, n=16 (6.8%).

In 16 cases, the autopsy reported OC as an incidental finding. The disease was not known before autopsy and was not the cause of death. Causes of death were as follows: cardiac disease, n=8; pneumonia, n=3; cerebrovascular disease, n=2; pulmonary embolism, n=1; sepsis, n=1; acute myeloid leukemia, n=1. The median age at OC diagnosis of these patients was 80 years (range: 56-92 years).

3. The diagnosis of primary OC at time of autopsy could no longer be upheld after pathologic review with current histopathological knowledge and techniques, n=24 (10.7%).

In these cases, which had been autopsied between 1975 and 1997, metastatic disease found during autopsy could be attributed to other primary tumors, and the site of the primaries could be identified retrospectively (colon, n=10; pancreas, n=5; stomach, n=2; extrahepatic bile ducts, n=1; cervix uteri, n=3; corpus uteri, n=1; breast, n=1; kidney, n=1). CDX2, CK7, CK20 and estrogen receptor were the most effective antibodies for discriminating primary OC from metastases to the ovary.

The median age of patients with ovarian metastases was 71 years (range: 47–88 years). In 12 of these cases, the patients died from tumor of unknown origin and the misinterpretation as “ovarian carcinoma” was made at autopsy. In 12 cases, the patient were wrongly diagnosed with OC while alive and were subsequently treated for this incorrect diagnosis.

4. Patients in whom OC was first diagnosed by autopsy and where death was directly due to OC in its final stage, n=37 (15.9%).

In these cases, the initial OC diagnosis was made on postmortem examination. Typical clinical diagnoses were “abdominal tumor of unknown origin”, “progressive cachexia”, or “suspected pulmonary embolism”. In only four of these 37 cases did the patient die at a gynecologic center. The remaining 33 patients died while in care of either the departments of internal medicine, departments of surgery or nursing homes. These 33 patients with newly diagnosed OC were 81 years old on average and significantly older than those patients in which the disease was diagnosed and treated during their lifetime by the local gynecologic center (60 years, $p<0.001$).

Table 2 demonstrates the OC incidence data reported by the local gynecologic center. It also shows the adjusted OC incidence in that the clinically data and the cases of patients who died of OC but diagnosis was firstly made by autopsy were grouped together. The autopsy cases comprised 8.8% of the adjusted OC cohort. The inclusion of the autopsy cases led to a slight but not significant increase in the median age of the cohort (60 years vs. 62 years, $p=0.70$). However, the proportion of elderly patients was significantly higher (≥ 80 years at OC diagnosis: 4.9% vs. 9.3%, $p=0.013$).

Discussion

With regard to epidemiology, three distinct subgroups of our autopsy cohort deserve further attention:

- A) Metastatic carcinoma diagnosed as primary OC

The ovary is a common site of metastases from other primary malignancies; the incidence of metastatic ovarian tumors has been reported with a wide range of 5-30% of all cancers occurring in the ovaries [14, 15]. The typical gross and histomorphologic features of these tumors were first clearly defined in the late 1990s [3-6]. In particular, tumors with a strong tendency to present in the pelvic cavity may mimic OC both grossly and histopathologically. In these difficult and unclear cases, misinterpretation as primary OCs were formerly not uncommon. In our study cohort, a review of the histopathological slides showed metastatic tumors in 10% of the cases of our cohort. These cases had been autopsied between 1975 and 1997. The primary tumor could be identified retrospectively by applying current histopathological knowledge and also in part by using modern immunohistochemical methods. Carcinomas of the gastrointestinal tract (75%) were the most common sources of ovarian metastases mimicking primary OC followed by other carcinomas of the genital tract (17%). The clinical relevance of these diagnostic pitfalls was comparatively small. Of the 24 cases in which the clinical and histopathological picture of ovarian metastases led to the erroneous diagnosis of primary OC, this only had clinical impact in 12 patients, i.e. the patients ran the risk of receiving an inappropriate therapy. Our data suggest that incidence and prevalence data of the 1970s-1990s may be adjusted because up to 10% of carcinomas in the ovary were, in fact, not properly classified.

B) The incidental findings

Previously undiagnosed carcinomas which were incidentally discovered on postmortem examination in women who died of other causes do not provide information regarding the incidence of the disease (number of new cases diagnosed in a population during a specific period) but might be of interest for studying the true prevalence of a disease (the number or proportion of people who have that disease in a specific period). These latent, asymptomatic and undetected tumors might be helpful for an improved understanding of carcinogenesis. In our autopsy cohort, approximately 7% of cases were exactly those cases. Unlike prostate cancer, which might be considered the most widely discussed malignancy with a significant gap between incidence and true prevalence of disease [16-18], we do not

think that the few incidental ovarian carcinoma findings offer new insights into the etiology, epidemiology or clinical management of OC. We also do not assume that there is a widespread presence of clinically insignificant disease in OC, as with prostate cancer. A multitude of autopsy studies on this subject have been published regarding prostate cancer, only a few on OC [7-12]. Most of these studies evaluated exclusively the metastatic patterns of the disease at the time of death [7, 9-12]. To our knowledge, our group reported the first data on latent OC in 2007 (however, these findings were not the actual topic of the previous paper and thus they were not discussed at that time) [8].

C) Patients in whom OC was first diagnosed by autopsy and in whom death was directly due to OC in its final stage

In order to provide an adjusted “real” OC incidence, we believe that these autopsy cases must be added to those who were diagnosed and treated at the gynecologic center. The autopsy sub-cohort (n=34 patients) comprised a distinct subgroup within the OC patients, namely elderly patients who obviously were judged as being inappropriate for oncological therapy; in fact, it even seems as if the need for making a correct diagnosis during their lifetime due to their age and/or condition was not considered important. The inclusion of these patients did not lead to a significant increase in the median age of OC patients (we observed only an increase of two years); however, resulted in an almost doubling of the number of the oldest patients, whom we defined as being ≥ 80 years of age at the time of OC diagnosis. These patients were not seen by specialized oncologists and thus play no role in their perception of the disease; nevertheless, with approximately 7% of the adjusted OC cohort these cases comprise an important part of the entity “ovarian carcinoma”.

Are our retrospective data important for addressing current or future questions regarding the etiology of OC? The two following aspects must be considered:

Firstly, geriatric gynecologic oncology is a new field to be explored. In the future, there will be more tailored and individualized strategies in the oncologic care of elderly patients which will reflect their functional age [19, 20]. With current standards of anesthesia and postoperative surveillance, it is possible for many elderly women to safely undergo OC

surgery, and only a minority of the patients must strictly be categorized as “inoperable” or “unfit for surgery”. In addition, the chemotherapy situation has changed in such a way that older women can receive regimens with safer profiles and might derive similar benefits as their younger counterparts. Progress in the oncologic care of elderly patients will lead to these patients being treated at gynecologic centers, and the number of patients in which the disease is firstly diagnosed at autopsy will decrease. Secondly, autopsy rates have dramatically decreased in many countries [21-24]. This is also reflected in our autopsy cohort. From the first decade of the study period (1975-1984), 91 cases were recruited; from 2002 to 2005 only five cases were recruited. Due to the reduced number of autopsies, important information leading to adjusted prevalence and incidence of OC data will probably be overlooked [24-27].

Conflict of Interest statement

The authors declare that there are no financial or personal relationships with other people or organizations that could inappropriately influence the work reported or the conclusions, implications, or opinions stated.

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Tables

Table 1: Four distinct subgroups within the autopsy cohort.

| | 1. OC known at time of autopsy | 2. OC not known at time of autopsy: incidental OC finding | 3. Metastases to the ovary (was diagnosed as OC at autopsy) | 4. OC not known at time of autopsy: death due to OC in final stage |
|------------------------------------|--------------------------------|---|---|--|
| 1975-2005, n=233: | 156 | 16 | 24 | 37 |
| 1975-1984, n=121 | 88 (72.7%) | 6 (5.0%) | 11 (9.1%) | 16 (13.2%) |
| 1985-1994, n=77 | 45 (58.4%) | 7 (9.1%) | 11 (14.3%) | 14 (18.2%) |
| 1995-2005, n=35 | 23 (68.6%) | 3 (8.6%) | 2 (5.7%) | 7 (20.0%) |
| Median age at OC diagnosis (range) | 69 years (24-96 years) | 80 years (56-92 years) | 72 years (59-88 years) | 81 years (59-98 years) |
| ≥80 years at diagnosis, n=58 | 25 (43.1%) | 9 (15.5%) | 2 (3.5%) | 22 (37.9%) |

Table 2: Ovarian carcinoma incidence. 1) Clinically evident incidence only; 2) Adjusted incidence including autopsy data.

| | 1975-1990 | 1991-2005 |
|--|-------------------------|-------------------------------|
| 1) OC diagnosed and treated at the gynecologic center ¹ | 234 | 193 |
| Median age at OC diagnosis | 61 years (range: 28-83) | 60 years (range: 23-91 years) |
| ≥80 years at OC diagnosis | 11 (4.7%) | 10 (5.2%) |
| 2) OC diagnosed and treated at the gynecologic center ² . | 231 | 190 |
| plus: | | |
| OC firstly diagnosed by autopsy, cause of death due to OC ³ | 20 | 13 |
| Median age at OC diagnosis | 81 years (range: 59-94) | 82 years (range: 70-98) |
| ≥80 years at OC diagnosis | 11 (55.0%) | 9 (69.2%) |
| <u>In total:</u> | 251 | 203 |
| Percentage of patients in whom OC was first diagnosed by autopsy | 8.0% | 6.3% |
| Median age at OC diagnosis (range) | 62 years | 61 years |
| ≥80 years at OC diagnosis | 22 (8.8%) | 20 (9.3%) |

OC: ovarian cancer

¹ Included were six cases which were diagnosed and treated at the Basel gynecologic center during this period; however, current pathological review showed that they were not primary OC, but rather metastases to the ovaries from other primaries.

² The above mentioned six cases were excluded from the adjusted incidence model.

³ From the entire autopsy cohort (n=37), we excluded those four patients who died at the gynecologic center.